

twenty (20) claims. As such, a check for \$7050.00 is enclosed herewith for the additional claims fees. The new claims do not add new matter. Accordingly, entry of the amendment is respectfully requested.

**1. Rejection of claims under 35 U.S.C. §112, 2<sup>nd</sup> paragraph**

The Official Action states that claims 1-17, 19 and 21 are rejected under 35 U.S.C. §112, 2<sup>nd</sup> paragraph as being indefinite. In particular, the Official Action states that certain claims contain the language “characterized in that” instead of the language “wherein”. Further, the Official Action states that claim 21 recites “mammals, including humans”, which is improper. Further, the Official Action states that certain claims identify a product by process and it is suggested that these claims be amended to recite the chemical compound.

**RESPONSE**

Applicants respectfully note that the rejected claims have been canceled without prejudice to or disclaimer of the subject matter contained therein. However, applicants further note that none of the newly introduced claims 22-183 contain the language rejected by the Examiner.

Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this rejection as none of the points of this rejection apply to the presently pending claims.

**2. Rejection of claims 15-17, 19 and 21 under 35 U.S.C. §102(b)**

The Official Action states that claims 15-17, 19 and 21 have been rejected under 35

U.S.C. §102(b) as being unpatentable over Amschler (US 5712298).

### **RESPONSE**

Applicants respectfully note that the rejected claims have been canceled without prejudice to or disclaimer of the subject matter contained therein. However, applicants further note that none of the newly introduced claims are “product by process” claims as were rejected claims 15-17 or depend from such claims, as did rejected claims 19 and 21.

Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this rejection as none of the points of this rejection apply to the presently pending claims.

### **3. Rejection of claims 1-17, 19 and 21 under 35 U.S.C. §103(a)**

The Official Action states that claims 1-17, 19 and 21 are rejected under 35 U.S.C. §103(a) as being unpatentable over Amschler. In particular, the Official Action states, in relevant part, that:

Amschler teaches the known roflumilast compound. The difference between the claimed process and the Amschler process is the molar ratio of the starting materials. The criticality of the molar ratio of the starting products is not disclosed. It would have been obvious to one of ordinary skill in the art to prepare the instant compound in a similar reaction process when the same chemical compound is obtained. Accordingly, the claimed process is an obvious variant therefrom.

To establish a *prima facie* case of obviousness, the PTO must satisfy three requirements. First, as the U.S. Supreme Court recently held in *KSR International Co. v. Teleflex Inc. et al.*, Slip Opinion No. 04–1350, 550 U. S. \_\_\_\_ (April 30, 2007), “a court

must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. ...it [may] be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. ...it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does... because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." (*KSR, supra*, slip opinion at 13-15.) Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

A *prima facie* case of obviousness must also include a showing of the reasons why it would have been obvious to modify the references to produce the present invention. See *Ex parte Clapp*, 277 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985). The Examiner bears the initial burden to provide some convincing line of reasoning as to why the ordinary skilled artisan would have found the claimed invention to have been obvious in light of the reference teachings. *Id.* at 974.

The Examiner has clearly failed to meet her burden of establishing a *prima facie*

case of obviousness since the cited reference does not teach or suggest each and every limitation of the presently pending claims. Further, there is no teaching contained in the cited reference which would motivate the skilled artisan to modify the teachings of Amschler to arrive at the presently pending claims.

The process of Amschler is taught as follows: (Example 5 prepared in analogy to Example 1)

A solution of 0.0275 mol of 3-cyclopropylmethoxy-4-difluoromethoxybenzoylchloride in tetrahydrofuran is added dropwise to a suspension of 0.03 mol of 4-amino-3,5-dichloropyridine and 0.066 mol of NaH (in mineral oil) in tetrahydrofuran at 15-20°C. The yield of final compound is 58.6% (Example 1).

The person skilled in the art having the task to make available a synthesis for roflumilast with high yield and high purity gets the following teaching from Amschler:

- 1 equivalent of 3-cyclopropylmethoxy-4-difluoromethoxybenzoylchloride is reacted with 1.1 equivalent of the anion of 4-amino-3,5-dichloropyridine; and
- the anion of 4-amino-3,5-dichloropyridine is produced by using 1 equivalent of 4-amino-3,5-dichloropyridine and 2.2 equivalents of the base NaH.

Such teaching leads to the following problems:

- The yield of the above-described process is much too low (58.6%);
- Tetrahydrofuran is not useful for technical purposes in large scale; and
- Sodium hydride is flammable and the liberation of hydrogen gas gives cause for major concerns such as explosions.

Applicants respectfully note that there is no teaching by Amschler that THF can be replaced by the solvents dimethylformamide or by N-methylpyrrolidone. Further, there is no teaching by Amschler that NaH could be replaced by KOtBu. Further, and as already conceded by the Examiner, there is no teaching by Amschler that an excess of the anion of 4-amino-3,5-dichloropyridine can be used to obtain a high yield or a high purity of roflumilast.

Absent some additional teaching, the prior art is clearly insufficient at rendering the presently claimed invention obvious. The prior art gives no guidance as to how the ordinary skilled artisan would arrive at the specifically claimed process limitations which produces roflumilast in higher yield and higher purity than previously taught by the prior art.

As such, the cited reference cannot establish a *prima facie* case of obviousness over the presently pending claims. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this rejection.

**CONCLUSION**

Based upon the above amendments and remarks submitted herewith, the presently claimed subject matter is believed to be novel and patentably distinguishable over the prior art of record. The Examiner is therefore respectfully requested to reconsider and withdraw the rejections and allow all pending claims. Favorable action with an early allowance of the claims pending in this application is earnestly solicited.

The Examiner is welcomed to telephone the undersigned attorney if she has any questions or comments.

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